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NEUROIMMUNOLOGICAL MECHANISMS OF THE FORMATION OF CHRONIC PAIN SYNDROME

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Abstract: Based on their origin, they distinguish between nociceptive, neurogenic (neuropathic) and psychogenic pain. Chronic low back pain can develop through all three pathophysiological mechanisms. The perception of damaging stimuli is carried out by nociceptors - pain receptors, which in the form of free nerve endings are widely represented in the skin, subcutaneous tissue, periosteum, joints, muscles, and internal organs.

Key words: prostaglandins, cytokines, biogenic amines, neurokinins.

The development of primary hyperalgesia is based on the phenomenon of nociceptor sensitization (increased sensitivity of nociceptors to the influence of damaging stimuli) due to the action of substances with a pro-inflammatory effect (prostaglandins, cytokines, biogenic amines, neurokinins, etc.). These substances come from damaged tissue, blood plasma, as well as from the peripheral terminals of C-nociceptors, interact with receptor proteins located on the membrane of nociceptors, trigger a cascade of biochemical reactions causing the development of “neurogenic inflammation”, dilation of blood vessels and an increase in their permeability, release from mast cells and leukocytes, prostaglandins, cytokines and biogenic amines. As a result, the nerve fiber becomes more excitable and more sensitive to external stimuli [1, 4]. Secondary hyperalgesia occurs as a result of central sensitization (increased excitability of nociceptive neurons in the structures of the central nervous system). The pathophysiological basis for the sensitization of nociceptive neurons in the dorsal horns of the spinal cord is the long-term depolarizing effect of glutamate and neurokinins released from the central terminals of nociceptive afferents due to constant intense impulses emanating from the area of damaged tissue, as well as the release of cytokines, chemokines and growth factors by glial and immune cells [4] . The resulting increased excitability of nociceptive neurons can persist for a long time, contributing to the expansion of the area of hyperalgesia and its spread to healthy tissue. In addition, there is an increase in the excitability of nociceptive neurons in the nuclei of the thalamus and somatosensory cortex of the cerebral hemispheres. Thus, peripheral damage

triggers a cascade of pathophysiological processes affecting the entire nociceptive system - from tissue receptors to cortical neurons, causing persistent changes in excitability in them, which are manifested by an increase in pain sensitivity. When the tissue heals, the phenomenon of peripheral and central sensitization will also disappear, and vice versa, the longer the damage persists, the longer the pain is felt [5]. Some studies have shown that the development of neuropathic pain is associated with cellular and molecular changes in the dorsal horn of the spinal cord, leading to the activation of microglial cells and astrocytes, and changes in pro- and anti-inflammatory cytokines [6–9]. The formation of referred muscle pain is associated with excitation of the spinal cord segments adjacent to those innervating the affected muscle, probably due to inactive synaptic contacts between the muscles and neurons of the corresponding spinal cord segments. The opening of these synapses during central sensitization leads to the excitation of neurons that do not normally respond to muscle afferentation, and pain can spread to neighboring areas related to the innervation zone of neurons that are anatomically not related to the affected muscle [10]. Neuropathic pain is pain resulting from direct damage to the somatosensory system [11]. Peripheral neuropathic pain (PNP) is the result of various influences, including traumatic nerve injury, diabetic neuropathy, HIV neuropathy, and drug-induced neuropathy [12]. Neuropathic pain is often caused by damage to the root due to its compression, edema, ischemia, and the formation of intraneural inflammation [13]; irritation of the root may be the result of the entry of chemical mediators and inflammatory cytokines formed during microdamage of a degenerative disc into the epidural space, which leads to the development of irritative pain syndrome without signs of disc herniation [14]. In addition, patients with compression radiculopathy often develop reflex musculoskeletal disorders, for example, muscular-tonic syndromes (in response to a change in motor pattern or to immobilize the affected motor segment), which, if persisted for a long time, can themselves become additional sources of nociceptive pain impulses [13]. The pathophysiological basis of neuropathic pain syndromes are disturbances in the mechanisms of generation and conduction of nociceptive signals in nerve fibers and the processes of controlling the excitability of nociceptive neurons in the structures of the spinal cord and brain [1]. Damage to nerves leads to structural and functional transformations in the nerve fiber: the number of sodium channels on the nerve fiber membrane increases, new atypical receptors and zones for generating ectopic impulses appear, mechanosensitivity occurs, and conditions are created for cross-excitation of dorsal ganglion neurons. All this forms an inadequate response of the nerve fiber to irritation, contributing to a significant change in the pattern of the transmitted signal. With myofascial pain syndrome, local ischemia develops in the spasmed muscle, which increases the activation of muscle fiber nociceptors. An increased flow of pain impulses from a given muscle, entering the cells of the dorsal horns of the corresponding segment of the spinal cord, increases the activity of the anterior motor neurons, which leads to even greater muscle spasm. Thus, muscle tension, which was initially protective and provided immobilization of the affected part of the spine, leads to the vicious circle of “pain - muscle spasm - pain” [15–17]. In patients with neuropathic pain, structural changes in the nociceptive system are more significant and include the formation of loci of ectopic activity in damaged nerves and pronounced changes in the integration of nociceptive, temperature and tactile signals in the central nervous system. In addition, the pathological processes observed in the nociceptive structures of the peripheral nervous system and the central nervous system are closely interrelated during the development of any pain syndrome. The death of inhibitory interneurons is noted, neuroplastic processes are initiated, leading to new interneuron contacts of tactile and nociceptive afferents, and the efficiency of synaptic transmission increases [18]. Under these conditions, the formation of a special pain symptom complex is observed, which is clinically manifested by a combination of negative and positive symptoms in the form of partial or complete loss of sensitivity (including pain) with the simultaneous occurrence in the affected area of unpleasant, often pronounced pain in the form of allodynia, hyperalgesia, dysesthesia , hyperpathies [19, 20]. Thus, neuropathic pain, in addition to the somatosensory one, also has a dysregulatory mechanism, in particular, there is a predisposition to the development of pathological processes that, when the structures of the somatosensory nervous system are damaged, lead to the occurrence of neuropathic

pain. This is indicated by data on the existence in rats of different genetic lines of high and low resistance to the development of neuropathic pain syndrome after transection of the sciatic nerve [21]. There is a certain dysfunction of the body's neuroimmunohumoral systems that are unable to provide adequate adaptation to stress [18, 22]. In addition, dysfunction of the serotonergic system is also important in the genesis of chronic pain syndromes [23]. The anti-pain effect of serotonin is realized by enhancing descending inhibition of segmental nociceptive input, the morphological substrate of which is serotonin. Great importance is attached to studying the functional state of the sympathetic-adrenal system in patients with acute and chronic pain syndromes, especially assessing the effectiveness of pain relief. In chronic pain syndrome, the sympathetic-adrenal system is activated. The excretion of adrenaline, norepinephrine and dopamine in patients depends on the nature of the chronic pain syndrome [25]. In recent years, a new direction has emerged in neurology that studies the gender aspects of chronic pain - gender neurology, based on an understanding of the role of sex hormones in the pathogenesis of any pain in both sexes, including, of course, chronic pain [26]. According to C.C. Palmeira et al. [27], gender influences pain perception and response to some classes of analgesics. Research conducted in recent years clearly demonstrates active and multidirectional interactions between all three types of sex hormones (estrogens, gestagens, androgens) in men and women in the mechanisms of pain reception and perception, which generally predetermines the currently known gender characteristics of chronic pain syndromes [28]. The nociceptive mechanism is involved in the formation of pain during the initiation of immune inflammation [29, 30]. There are immunological mechanisms for the development of RPL, which are triggered by an inflammatory reaction and activation of glial cells in the corresponding segments of the spinal cord [31, 32]. A certain role in the development of RPL belongs to specific proteins, for example, the interaction of CD200 (a membrane glycoprotein from the immunoglobulin superfamily) with its receptor CD200R plays a significant role in maintaining the balance of microglial cells; their imbalance is important in the pathogenesis of neuroinflammatory and neurodegenerative diseases [4, 33]. Experimental studies have shown that intrathecal administration of CD200R1 to rats causes a rapid attenuation of glial activation and the synthesis of proinflammatory cytokines in the spinal cord, which leads to a decrease in neuropathic pain after experimental nerve injury [31]. Thus, various mechanisms are involved in the formation of pain; the immunological component plays an important role in the chronicization of pain, which must be taken into account when studying the pathogenesis of the disease and choosing therapy.

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